Some things you always wanted to know about clinical trials but were afraid to ask

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The views are not necessarily an official position of the FDA

What are Phase 1, 2, 3, and 4 trials?

- Phase 1 - first trial in humans
  - Designed to estimate a maximum tolerated dose.
  - Small number of patients (3 to 10 per dose)
    - Total number of patients typically fewer than 50
  - Usually dose escalation: work from a low dose to a higher one, until toxicity is observed
  - Estimate toxicity as a function of dose (or log(dose))

Phase 2

- Phase 2 studies evaluate biologic activity and adverse event rates
  - Determine adequate response rate (e.g., at least 20% of patients will respond)
  - Find the right dose / schedule
    - Serum levels of drug?
    - Trough levels
  - Generally fewer than 100 patients

Phase 2 (2)

- Preliminary ideas on adverse event rates - since studies are small, estimates of rates are imprecise
  - Standard deviation proportional to $1/\sqrt{n}$
  - Studies usually not comparative, so don't know if the rate is too high, or just characteristic of the disease

Phase 3

- **Comparative** trial to evaluate drug
  - Comparator group important - Standard of care, Placebo, never nothing in serious or life-threatening diseases (ICH E3, E9, E10)
  - Endpoint - must be clinically relevant to disease (e.g., reduce mortality, reinfarction, agreed on criteria such as ACR20, etc.)
    - Should be validated as relevant in the disease

Phase 3 (2)

- Sample size depends on level of type I error, type II error, variability of response, anticipated difference between treatment and control
- Use of subgroups (strata) may make comparison more precise
- Analysis plan must be specified *a priori*

Phase 4

- Post-marketing surveillance
  - Mostly Passive reporting
  - Subject to biases
  - Sometimes FDA will require an epidemiological study post-marketing (e.g., Varivax or Carticel)

How is the patient enrollment size determined for each site?

- History at the site for diagnosing patients for the specific disease (for conditions matching those in the trial) - e.g., a stage 3 cancer trial might not be easily conducted in a rural primary care setting
- Randomize within site, so don't want sites with very few patients
- Also may stratify by prognostic factors (sex, age, stage of disease)

What if site doesn't meet enrollment targets?

- Study may need to add additional sites to reach sample size goals
- Possibility of imbalance in the randomization
- Future studies may decide not to use the under enrolling site

How does sponsor combine data from multiple sites?

- Statistical models must account for possible differences in the sites (e.g., different care patterns, etc.), as well as other strata
  - This is called stratification or blocking. Statistical methods are well-developed for this
  - Subtract the mean of the response at the site from all measurements. This aligns the adjusted response.

Combining data across sites

- Potential problem:
  - If sites have different responses to treatment (called a treatment by site interaction), we have a problem
  - In one study, one site had a large positive treatment effect, while three others showed no difference. Led to discovery of other problems
- For global trials, the situation is essentially the same

What data will be included in the licensing application?

- Study reports that will comprise the submission (phase 1, 2, 3 studies) need to be submitted.
  - Negotiate with FDA regarding early phase studies
  - All phase 3 studies will be required - can't just show 2 positive studies and ignore 10 negative ones

Data in marketing application

- Need to show all efficacy data from primary, secondary, and tertiary endpoints
  - If a composite endpoint is used, it's useful to include the components of the composite.
- Safety data
  - All AEs include mild, moderate, severe, deaths
  - If product is a member of a known class, some events are expected and won't be a problem unless they are excessive

Marketing application information

- Include the final revision of the protocol
  - Should be dated before the data are unblinded
  - Non-protocol analyses will be considered exploratory and may be useful for labeling, but not for showing an indication

Who decides on the CRF fields? Why fill in all the fields?

- Usually decided by clinicians from the sponsor with input from FDA clinicians
- Need all fields completed to show that the information was sought (either by question or lab test) and negative, or not done. A blank field does not distinguish.

If a patient leaves the trial, does their data still count?

- Data always count - intention-to-treat means that these patients should be followed, if possible.
- Excluding such patients means that the patients who do poorest won't affect the study - not a good idea

Define some statistical terms

- Blinding (double) - means that neither the patient nor the evaluator knows what treatment has been given. Very important when subjective endpoints are involved.
  - Not always possible if different schedules or side effects of drugs are characteristic of treatments

Definitions (2)

- Randomization - ensures that patients are given treatment in such a way that no investigator bias is involved. There must be no way the study personnel know what treatment the next patient will receive.
  - When this principle has been violated, studies have been discounted and had to be repeated.

Definitions (3)

- Adequate and Well-controlled study - this refers to the way the study has been conducted:
  - Was it randomized?
  - Was it blinded if possible?
  - Was the control group appropriate?
    - Patients comparable at baseline?
    - Control treatments given at labeled levels?

Definitions (4)

- Control groups (ICH E10) are a crucial part of a trial.
  - FDA expects that the patient population will be split into new treatment and “not new treatment” groups
  - Concurrent placebo control - compares standard of care + placebo with standard of care + active treatment

Definitions (5)

- Controls (continued)
  - Concurrent no-treatment control - compares no treatment group with active treatment group (may not be ethical in all cases) and is difficult to blind
  - Concurrent active control - compares active control with treatment - may wish to show non-inferiority

Definitions (6)

- Historical control
  - only in unusual circumstances - lack of concurrency, possible different entry criteria,
  - Patients may not be comparable

How does coding aid the analysis?

- I prefer to have raw data submitted to the sponsor and they code it later rather than have sites do it
  - Consistency in coding
  - Possible to retrieve the underlying data
  - Text coding may be useful to retrieve common problems that arise

What do you do with comment fields and unsolicited text?

- These are used mostly for safety analyses by clinical reviewers.
  - If there are repeated comments at many sites, they may be encoded and analyzed
  - Sponsor may audit records at sites to determine if some “unsolicited events” are really more common

How are protocol/trial considerations determined?

- The indication the sponsor wants tends to be the main determinant. FDA will sometimes differ with what the right endpoint is, what the right trial is, etc.
- The size and duration of the treatment effect will determine sample size, number of sites, and duration of follow up, etc.

Why can’t we vary from the protocol?

- It opens the door to fraudulent practice
  - Sponsor and investigator have agreed to do a certain trial and deviations from that are not allowed
- If protocol isn’t followed, we have no idea what the trial has shown - some sites may have admitted one sort of patient, others another; some may deliver one sort of treatment, others another

Why follow protocol? (2)

- FDA will not accept trials with many protocol deviations
  - Require sponsor to redo the trial
- If small number of deviations relative to the sample size, usually not a problem, but large numbers suggest systematic issues and can get an investigator disbarred
- “Almost eligible” is still a violation - don’t do it

How do statisticians contribute to the regulatory review?

- They review the data analyses and replicate major analyses
- Ensure that proper analyses were done
- Do new exploratory analyses (useful for labeling, or checking unexpected outcomes)
- Check data for usability

What is expected of investigators and monitors?

- Carry out the protocol exactly
- Submit data that are internally consistent
  - Proper links among files
  - Values lie within appropriate ranges
  - Reduce missing values to a minimum (follow patients after dropout, etc.)
  - Don't falsify any data - if discovered, all data from the site may be discarded

When/why does a sponsor perform an interim analysis?

- Why?
  - Stop early for a safety problem
  - Stop early because drug doesn’t work
  - Stop early because drug works
- When?
  - Timed by fraction of patients enrolled, fraction of events observed

Interim analysis (2)

- Plan analyses
  - State number (usually not too many, =5)
  - Ensure that blindness is maintained (DSMB usually needed)
  - Adjust significance levels (O'Brien-Fleming, Haybittle-Peto, Pocock, Bonferroni)

Break blind if patient has AE?

- Yes - should do for patient's safety, especially if a serious AE has occurred
- Patient is usually removed from the study and treated as a failure
- Because blind is broken in these cases, it's important that treatments be indistinguishable - should look alike, smell alike, etc.

How does FDA decide what goes on product label?

- The results of all the trials go into the product label. The FDA gives the interpretation.
  - Advertising and promotion are major issues, so the wording of the label is key
- AEs are usually listed in decreasing order of frequency, but not below a given percent (may vary depending on product and trial experience)

Finale

- These comments give a brief introduction to regulatory aspects of clinical trials
- Further information available at
  - www.fda.gov - has guidance documents with a lot of information on regulations, requirements
  - www.ich.org - provides International Conference on Harmonization documents; see E3, E9, E10 for material on clinical trials